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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/585,566	08/29/2006	Robert C. Moschel	253443	3649

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EXAMINER	
JAISLE, CECILIA M	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
12/09/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/585,566	MOSCHEL ET AL.	
	Examiner	Art Unit	
	Cecilia M. Jaisle	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,31,32,40,41 and 49-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-17,40,41,49-59 and 62-64* is/are allowed.

6)☒ Claim(s) *31,32,60 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31, 32, 60 and 61 are rejected under 35 U.S.C. 112, paragraph 1, because the specification, while enabling for human O^6-alkylguanine-DNA alkyltransferase inactivation *in vitro*, does not reasonably provide enablement to treat mammalian cancer cells by administering a claim 1 compound or salt with an antineoplastic alkylating agent that causes cytotoxic lesions at the DNA guanine residue O^6-position. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Many if not most cancers said to be treated by the claimed methods are known as difficult to treat. Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses.

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed

invention must have a specific and substantial utility." See also MPEP 2163, *et. seq.* This disclosure is not sufficient to enable the claimed methods based solely on the disclosed inactivation of human O^6-alkylguanine-DNA alkyltransferase *in vitro*.

MPEP § 2164.01(a) states:

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction provided by the inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed. Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

1. **Breadth of the claims:**

(a) Scope of the methods. The claims cover methods using 2-amino-O4-substituted pteridines and antineoplastic alkylating agents that cytotoxic lesions at the DNA guanine residue O^6-position in cancer treatments as mentioned above.

(b) Scope of the diseases covered. The claims cover methods to treat any and all mammalian cancer cells.

Cancer includes colon, prostate, brain, breast, ovarian, lung, stomach cancers, lymphoma, leukemia, Wilms' tumor rhabdomyosarcomas, multiplemyeloma, soft-tissue sarcomas, Hodgkin's and non-Hodgkin's lymphomas and many others.

- Colon cancers include many types which are rather diverse. Most are adenocarcinomas, either of the mucinous (colloid) type or signet ring type. Less common colon cancers include squamous cell, neuroendocrine carcinomas, carcinomas of the scirrhous type, lymphomas, melanomas (primary or meta-static), sarcomas (fibrosarcomas and Leiomyosarcomas) and Carcinoid tumors.
- Prostate carcinomas are usually adenocarcinomas, but others include small cell, mucinous, prostatic ductal, basal cell, neuro-endocrine, signet-ring cell carcinomas, squamous cell carcinoma of the prostate and others.
- Breast cancers come in great variety. The most important category of breast cancers is the ductal cancers, which come in a wide variety of types, divided into categories: intraductal (*in situ*); invasive with pre-dominant intraductal component; invasive, NOS; comedo; inflammatory (IBC); medullary with lymphocytic infiltrate; mucinous (colloid) carcinoma; papillary carcinoma; scirrhous; tubular and others. Ano-

ther category is lobular breast cancers: *in situ*, invasive with predominant *in situ* component and invasive. Paget's disease of the nipple can be also with intraductal carcinoma or with invasive ductal carcinoma. Adenomyoepithelioma is dimorphic tumor characterized by the presence of both epithelial and myoepithelial cells. There is breast angiolipoma and spindle cell lipoma of the breast. There is lymphoma of the breast (both Non-Hodgkin's lymphoma of the breast and Hodgkin's disease of breast forms). There are some sarcomas, including giant cell sarcoma of the breast, leiomyosarcoma of the breast, Angiosarcoma of the breast, cystosarcoma phylloides and liposarcoma of the breast. There are carcinoid tumors that can be primary carcinoid tumors of the breast or can arise from nonmammary sources. There are breast salivary gland-like tumors, including acinic cell carcinoma, oncocytic carcinoma (Mammary epithelial oncocytoma) and mucoepidermoid carcinoma. Other rare carcinomas include Spindle cell carcinoma of the breast, Squamous cell carcinoma of the breast, Secretory Carcinoma of the Breast (Juvenile secretory carcinoma), Metaplastic carcinoma of the breast (a heterogeneous group of invasive breast cancers including types with squamous differentiation and those with heterologous elements), Invasive Micropapillary Carcinoma of the Breast, Adenoid cystic carcinoma of the breast, cribriform carcinoma, Myofibroblastoma of the Breast (Benign spindle stromal tumor of the breast) and glycogen-rich clear cell carcinoma of the breast. There are numerous other rare breast cancers, including, e. g., Fibromatosis of the breast (extra-abdominal desmoid), Angiomatosis of the Breast and mammary hamartoma. There are also nonmammary tumors, primarily adenocarcinomas, that

can metastasize to the breast, including bronchogenic carcinomas, malignant melanomas (primary and secondary), rhabdomyosarcomas, malignant mesotheliomas, thyroid carcinomas, renal cell carcinomas, malignant lymphomas and gastrointestinal carcinomas (including those from the stomach, pancreas, esophagus and colon).

The specification fails to identify the results of treatment with the methods of this invention and how such results would be recognized, particularly with regard to conditions and diseases that are currently considered incurable, untreatable or fatal.

2. **Nature of the invention and predictability in the art:** The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present:

> The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

Plant Genetic Systems v. DeKalb Genetics Corp., 65 USPQ2d 1452 (CAFC 2003).

3. **Direction and Guidance:** That provided is very limited. The dosage range information is meager at best. It is generic, the same for all disorders the specification covers. No specific direction or guidance provides a regimen or dosage effective specifically for all of the conditions construed by the claims.

4. State of the prior art: The art indicates the need for undue experimentation.

Schold, et al., Neuro-Oncology, Jan. 2004, 28-32, reports only the beginning of clinical trials:

> Although only marginally effective in most cases, drugs that alkylate DNA in the O^6-position of guanine are the agents most commonly used against anaplastic gliomas. These include the nitrosoureas, procarbazine, and temozolomide. Resistance to cytotoxic effects of these agents is mediated in large part by the DNA repair protein O^6-alkylguanine-DNA alkyltransferase (AGT). AGT can be transiently suppressed by the exogenous administration of O^6-benzyl-guanine (BG), which binds to and inactivates the repair protein. During the period of suppression and until new AGT protein is synthesized, the cells in which AGT has been suppressed are dramatically more sensitive to DNA alkylating drugs. Consequently, BG has entered clinical trials in combination with carmustine, a representative alkylating agent.

Javanmard, et al., J. Med. Chem., 2007, Vol. 50, # 21, 5193-5201, summarized the limited ability of tested compounds to sensitize cells to alkylating agents:

> Despite the excellent alkyltransferase inactivation activity of the folate esters describe in this paper, their ability to sensitize cells to alkylating agents was limited. This is most likely due to a low level of uptake rather than rapid degradation because their conversion to folate by cellular esterases was quite slow. However, they provide a very useful lead for the design of other highly water soluble, specific, and potent alkyltransferase inhibitors based on the ability to interact with additional residues in the alkyltransferase active pocket.

Thus, ability of an agent that inactivates O^6-alkylguanine-DNA alkyltransferase to treat all cancers the claims recite remains open to further study and proof. The ability of any antineoplastic agent that causes cytotoxic lesions at the DNA guanine residue O^6-position to treat all cancers also remains open to further study and proof.

Dolan, et al., Cancer Research 51, 3367-3372, July 1, 1991, report:

> Our results demonstrate that O^6-benzylguanine, O^6-(p-chlorobenzyl)guanine, and O^6-(p-methylbenzyl)guanine can be used to enhance the cytotoxicity of chloroethylating and methylating agents which react at the O^6 position of cellular DBA guanine residues. An analysis of several tumor cell lines including human brain, melanoma, lymphoma, and colon have illustrated a correlation between the extent of enhancement and the amount of alkyltransferase.

Thus, Dolan recognizes that, even with the addition presence of an antineoplastic agent that causes cytotoxic lesions at the DNA guanine residue O^6-position, the claimed methods will not treat all mammalian cancers.

5. **Working Examples:** Applicants do not provide highly predictive competent evidence or recognized tests to treat all conditions recited for the claims. Furthermore, Applicants have not provided competent evidence that the instantly disclosed tests are highly predictive for all uses disclosed and embraced by the claim language for all of the intended hosts.

6. **Skill of those in the art:** Ishiguro, Schold and Javanmard call into question the efficacy of treatment with the claimed methods. Dolan calls into question the efficacy of antineoplastic agents that cause cytotoxic lesions at the DNA guanine residue O^6-position, to treat all mammalian cancers. The references discussed above confirm the need for additional research.

7. **Quantity of experimentation needed to make or use the invention.** Based on the disclosure's content, an undue burden would be placed on one skilled in the pharmaceutical arts to use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for reasons explained

above. The state of the art, as discussed in the articles above, indicates the requirement for undue experimentation, particularly with regard to potentially devastating side effects. Thus, the ability of an agent that inactivates O^6-alkylguanine-DNA alkyltransferase to treat all of the diseases construed by the present claims remains open to further study and proof.

See MPEP 2164.01(a), discussed *supra*, justifying the conclusion of lack of enablement commensurate with the claims. Undue experimentation will be required to practice Applicants' invention.

Remarks to Response of 04-23-2009

Applicants state, "There is no question relating to the efficacy of antineoplastic alkylating agents in treating cancer." This is not true. The Dolan reference, cited and discussed above, exemplifies a limited number of cancers in which antineoplastic alkylating agents are a recognized treatment. Antineoplastic alkylating agents are a class of drugs that differ from other alkylating agents used clinically in that they are monofunctio-nal and unable to cross-link cellular macromolecules. Among their common properties are a requirement for metabolic activation to intermediates with anti-tumor efficacy and the presence in their chemical structures of N-methyl groups that, after metabolism, can covalently modify cellular DNA. The precise mechanisms by which each of these drugs acts to kill tumor cells are not completely understood. Antineoplastic alkylating agents produce a wide range of assorted toxic and other untoward side effects.

Accordingly, Claims 31, 32, 60 and 61 are properly rejected under 35 USC 112, paragraph 1, and this rejection is deemed sound.

Allowed Claims

Claims 1-17, 40, 41, 49-59 and 62-64 are allowed. The previous Office Action gives reasons for allowing these claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle, J.D. whose telephone number is 571-272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the

examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. If you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia M. Jaisle/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, AU 1624